Add new claims 28 and 29 as follows:

-- 28. A pharmaceutical composition comprising the purified human SDF-5 protein of claim 19 and a pharmaceutically acceptable carrier.

B3 29. A purified human SDF-5 polypeptide comprising an amino acid sequence selected from the group consisting of:

(a) amino acids 1, 18, 19, 20, 21, 22, 23, 24 or 25 to 295 of SEQ ID NO: 2; and

(b) amino acids 1 to 275 of SEQ ID NO:3. --

REMARKS

The claims are 18-20, 22, 23 and 25. Claims 18 and 20 have been amended to more particularly point out and distinctly claim what Applicants consider to be the invention. Claims 28 and 29 have been added to claim specific embodiments of the invention. No new matter has been added, and no new issues are raised by the claims. The claims relate to purified human SDF-5 polypeptides comprising the amino acid sequences of SEQ ID NO: 2 or SEQ ID NO: 3; purified human SDF-5 proteins produced by culturing a cell transformed with a DNA comprising the nucleotide sequence of SEQ ID NO:1, and recovering and purifying protein from the culture medium; and pharmaceutical compositions comprising a human SDF-5 polypeptide.

The claims as now presented are reproduced in Exhibit A attached hereto for the Examiner's convenience.

Rejection Under Section 112, First Paragraph

Claim 20 was rejected under 35 U.S.C. § 112, first paragraph, for a perceived lack of enablement due to a lack of *in vivo* data demonstrating the effects of the claimed compositions. For the following reasons, the rejection is respectfully traversed.

The rejection of claim 20 appears to be based upon the premise that, without *in vivo* results in the specification, claims to compositions comprising therapeutic amounts of the human SDF-5 polypeptide cannot be enabled. This premise is erroneous. The Federal Circuit Court of Appeals has specified that the PTO should accept the truthfulness of statements in the disclosure in the absence of sound reasoning and evidence establishing a *prima facie* case refuting the disclosed uses of the invention. *In re Brana*, 34 U.S.P.Q. 2d 1436, 1440-1441 (Fed. Cir. 1995); *see also, In re Marzocchi*, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971); *In re Strahilevitz*, 212 U.S.P.Q. 561, 563 (C.C.P.A. 1982). The present specification contains disclosure of *in vivo* utility, supported by an experimental demonstration of related *in vitro* utility. The specification discloses that human SDF-5 protein may be used to treat a number of tissue defects, and healing and maintenance of various types of tissues and wounds. The tissues and wounds which may be treated include cartilage, but may also include, for example, epidermis, nerve, muscle, including cardiac muscle, other connective tissue, such as bone, tendon and ligament. These methods, according to the invention, entail administering to a patient needing such tissue formation, wound healing or tissue repair, an effective amount of human SDF-5 protein. The human SDF-5 containing compositions may also be used to treat or prevent such conditions as rheumatoid

arthritis, osteoarthritis, and other abnormalities of cartilaginous, or other organs or tissues. The specification also contains experiments which demonstrate activity of human SDF-5 *in vitro* in suitable cell populations, demonstrating that human SDF-5 has the projected effects. Thus, the burden is upon the PTO to establish a *prima facie* case of nonenablement, which it has failed to do.

The assertion that the instant specification provides "insufficient guidance" to "predict the efficacy of the claimed therapeutic compositions with a reasonable expectation of success" is incorrect. The specification is replete with disclosure of the therapeutic effects of human SDF-5. At page 19 of the specification, it is disclosed that human SDF-5 has application in the induction, formation, growth, differentiation, proliferation and/or maintenance and healing of cells and tissues such as chondrocytes and/or cartilaginous tissue, as well as pancreatic tissue, and other organ tissues, in humans and other animals. Such a preparation employing human SDF-5 protein may have prophylactic use in treatment of rheumatoid arthritis and osteoarthritis and traumatic injury to cartilage, as well as preventing pancreatic tumors, diabetes and other pancreatic tissue disorders. It is further disclosed, on pages 19 and 20, that human SDF-5 proteins may be used in wound healing and in related tissue repair. The preparation and formulation of therapeutic compositions comprising human SDF-5 is described on pages 21 and 22, and the dosage regimen for administration of SDF-5 is described on page 22. Moreover, Example 3 of the specification describes the Rosen-modified Sampath-Reddi assay, which provides an *in vivo* assay for evaluating bone, cartilage, and/or other connective tissue activity of SDF-5.

There is nothing in the record to establish that undue experimentation is required to determine the optimal dosage or mode of administration and thereby achieve the disclosed result. Given Applicants' disclosure of the uses and methods for evaluating efficacy, combined with knowledge generally available in the medical field, undue experimentation is not required to select an optimal dosage. *See In re Skuballa*, 12 U.S.P.Q.2d 1570 (B.P.A.I. 1989). Further, the Examiner should recognize the high level of skill attained by the medical practitioners who will be practicing the invention. The experimentation and judgment necessary for determination of optimal dosage and administration of therapeutical agents is the type of decision that practitioners make routinely and does not require undue experimentation.

The assertion that the specification is non-enabling because no examples are provided is inconsistent with the standards set forth by the Court of Appeals for the Federal Circuit. In the case of *In re Wright*, 27 U.S.P.Q.2d 1510 at 1513 (Fed. Cir. 1993), the C.A.F.C. stated that all that is required is objective enablement. Thus, under 35 U.S.C. §112, it is irrelevant whether this teaching is provided through broad terminology or illustrative examples. *Id.*

The Examiner next argues that Applicants' claims are insufficient because Applicants have not disproved the existence of a number of highly speculative disadvantages, such as the SDF-5 protein being proteolytically degraded, suffering from a short serum half-life, or being unable to penetrate tissues or cells where its activity is to be exerted. These arguments are based upon mere speculation, and there is no support for the Examiner's suspicion that such disadvantages actually exist.

As discussed above, Applicants have provided ample teachings in their specification that human SDF-5 has biological activity for the induction, formation, growth, differentiation, proliferation and/or maintenance and healing of cells and tissues such as chondrocytes and/or cartilaginous tissue; and is effective in treating or preventing a number of tissue disorders. Moreover, Applicants have provided additional guidance as to some factors the skilled practitioner might take into account when determining the optimal dosage and in monitoring the progress of the patient (see page 22 of the specification). Applicants have fully enabled one of skill in the art to make and use a composition comprising an effective amount of SDF-5 protein, without undue experimentation, and the rejection of claim 20 should be withdrawn.

Rejections Under Section 112, Second Paragraph

Claims 18 and 20 were rejected as being indefinite in the recitations of "according to" and "at least one human SDF-5 polypeptide," respectively. These rejections have been obviated by the amendments to claim 18 and 20.

Provisional Double-Patenting Rejection

The provisional double-patenting rejection stated in the Office Action is noted.

With respect to co-pending application USSN 08/848,439, Applicants have made an election in this application for examination of claims directed to nucleotide sequences of SEQ. ID 1 and 2, and related materials, so that claims pertaining to polypeptides and compositions are not

being examined in that application. Further, as noted by the Examiner, none of the claims in the other application upon which the rejection is based have been allowed, making the possibility of double patenting no impediment to the claims pending in the present application.

Withdrawal of the double-patenting rejection is requested.

Rejection Under Section 102

Claims 18, 23 and 25 were rejected under 35 U.S.C. § 102(a) as anticipated by Shirozu et al., on the basis that Shirozu et al. teach an SDF-5 protein with "100% sequence identity" to SEQ. ID NO:3. Applicants respectfully traverse this rejection.

The sequence alignment provided by the Examiner demonstrates 97.6 to 97.8% sequence identity between the mouse SDF-5 polypeptide disclosed in Shirozu et al. and the human SDF-5 polypeptide of SEQ ID NO:3. Because the mouse polypeptide sequence of Shirozu et al. is not identical to the claimed human SDF-5 polypeptide, the rejection is improper.

Withdrawal of the rejection under 35 U.S.C. § 102(a) is respectfully requested.

Rejection Under Section 103

Claims 18, 19, 20 and 22 were rejected under Section 103 as being unpatentable over Shirozu et al. For the reasons cited below, the rejection is respectfully traversed.

Although the Examiner is correct that the cited reference discloses an SDF-5 protein which may contain an N-terminal signal sequence, this reference contains no teaching or suggestion of

the specific sequence claimed by Applicants. A proper rejection under Section 103(a) must present a prima facie case as to why the specifically claimed subject matter would have been obvious to those skilled in the art.

> To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. MPEP 2143.03 (emphasis added)

Since the cited references contain no teaching or suggestion of the specifically claimed sequences, the disclosure of a common feature is insufficient to sustain the rejection. Withdrawal of the rejection under Section 103(a) is requested.

CONCLUSION

In view of the foregoing remarks and amendments, Applicants respectfully request issuance of pending claims 18-20, 22-23, 25 and 28-29. Should the Examiner believe that a telephonic interview would assist in clarifying any remaining issues, or to otherwise expedite prosecution, Applicants respectfully invite the Examiner to call the undersigned attorney at the telephone number provided below.

If any fee is due with regard to this paper, Applicants hereby authorize payment of such fee from Deposit Account No. 07-1060.

Respectfully submitted,

Barbara A. Gyure

Barbara A. Gyure
Reg. No. 34,614
Attorney for Applicants
(617) 498-8653

Genetics Institute, Inc.
87 CambridgePark Drive
Cambridge, MA 02140

EXHIBIT A
USSN 08/949,904
Claims as Presented November 19, 1998

18. (Once amended) A purified human SDF-5 polypeptide comprising an amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 3.

19. (Once amended) A purified human SDF-5 protein produced by the steps of

(a) culturing a cell transformed with a DNA molecule comprising the nucleotide sequence from nucleotide #316 to #1143 as shown in SEQ ID NO:1; and

(b) recovering and purifying from said culture medium a protein comprising the amino acid sequence from amino acid #21 to amino acid #295 as shown in SEQ ID NO:2.

20. (Once amended) A composition comprising a therapeutic amount of the human SDF-5 protein according to claim 19.

22. A purified human SDF-5 protein comprising the amino acid sequence from amino acid #1 to #295 of SEQ ID NO:2.

23. A purified human SDF-5 protein comprising the amino acid sequence from amino acid #1 to #275 of SEQ ID NO:3.

25. A purified human SDF-5 protein having a molecular weight of about 30 to about 35 kd, said protein comprising the amino acid sequence of SEQ ID NO:3 and having the ability to regulate the transcription of one or more genes.

28. (NEW) A pharmaceutical composition comprising the purified human SDF-5 protein of claim 19 and a pharmaceutically acceptable carrier.

29. (NEW) A purified human SDF-5 polypeptide comprising an amino acid sequence selected from the group consisting of:

(a) amino acids 1, 18, 19, 20, 21, 22, 23, 24 or 25 to 295 of SEQ ID NO: 2; and

(b) amino acids 1 to 275 of SEQ ID NO:3.